

FORM PTO-1390 (Modified)
(REV 10-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

BDA-0038

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/171885

INTERNATIONAL APPLICATION NO.
PCT/US97/07491INTERNATIONAL FILING DATE
02 May 1997PRIORITY DATE CLAIMED
03 May 1996

TITLE OF INVENTION

PRODRUG COMPOSITIONS AND DRUG DELIVERY METHODS USING SYNTHETIC RECEPTORS

APPLICANT(S) FOR DO/EO/US

CUBICCIOTTI, Roger S.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

Executed Verified Statement Claiming Small Entity Status

"EXPRESS MAIL" Mailing Label No. EL002434340USDate of Deposit 28 October 1998

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D. C. 20231

Suzanne Sparkman
(MAILER)

Suzanne Sparkman
(SIGNATURE)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO PCT/US97/07491	ATTORNEY'S DOCKET NUMBER BDA-0038
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20. The following fees are submitted:				CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :					
<input type="checkbox"/>	Search Report has been prepared by the EPO or JPO		\$930.00		
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482)		\$720.00		
<input type="checkbox"/>	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))		\$790.00		
<input type="checkbox"/>	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO		\$1,070.00		
<input checked="" type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)		\$98.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$98.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				\$0.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	8 - 20 =	0	x \$22.00	\$0.00	
Independent claims	4 - 3 =	1	x \$82.00	\$82.00	
Multiple Dependent Claims (check if applicable). <input type="checkbox"/>				\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$180.00	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). <input checked="" type="checkbox"/>				\$90.00	
SUBTOTAL =				\$90.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				\$0.00	
TOTAL NATIONAL FEE =				\$90.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3 28, 3.31) (check if applicable). <input type="checkbox"/>				\$0.00	
TOTAL FEES ENCLOSED =				\$90.00	
				Amount to be: refunded	\$
				charged	\$

- ☒ A check in the amount of **\$90.00** to cover the above fees is enclosed.
- ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **12-1086** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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NAME

32,257
REGISTRATION NUMBER

28 October 1998
DATE

Attorney Docket No.: BDA-0038
Inventor or Patentee: Roger S. Cubicciotti
Serial or Patent No.: PCT/US97/07491
Date Filed or Issued: 02 May 1997
Title: Prodrug Compositions and Drug Delivery
Methods using Synthetic Receptors

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(b)) - INDEPENDENT INVENTOR**

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled **Prodrug Compositions and Drug Delivery Methods using Synthetic Receptors** described in

() specification filed herewith.

(XX) international application no. PCT/US97/07491, filed 02 May 1997.

() patent no. _____, issued _____.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

(XX) no such person, concern, or organization

() person, concerns or organizations listed below*

***NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)**

FULL NAME:

ADDRESS:

() INDIVIDUAL () SMALL BUSINESS CONCERN () NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Roger S. Cubicciotti

NAME OF INVENTOR


Signature of Inventor

10/21/98
Date

PRODRUG COMPOSITIONS AND DRUG DELIVERY METHODS
USING SYNTHETIC RECEPTORS

INTRODUCTION

This application is related to Disclosure Document No.
5 353687, received May 6, 1994 entitled "Smart drugs: prodrug
compositions and drug delivery methods using synthetic
receptors".

BACKGROUND OF THE INVENTION

Research in drug delivery technology continues to
10 escalate as innovative delivery systems are found in many cases
to offer advantages over conventional drug formulations. For
example, alternate drug delivery systems have been shown to
provide therapeutic advantages by increasing efficacy and
safety, while reducing side effects. Many of these systems
15 offer usage benefits to the patient, including more convenient
dosage forms and administration schedules. In addition,
alternate delivery systems enable new indications for approved
drugs, including generics. Further, the development of new
drug delivery systems has expedited approval and widespread use
20 of many new drugs in development. Accordingly, the worldwide
market for alternate drug delivery systems has more than
doubled over the past five years to approximately \$6 billion,
and annual growth rates averaging 30% to 40% have been
projected for the next several years. Examples of FDA-approved
25 drug delivery systems include polymers, osmotics, liposomes,
nasal and transdermal formulations, aerosols and resins.

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Emerging delivery systems include gels, foams, microparticles, red blood cells and prodrugs. In addition, many device technologies are being developed to improve the efficiency and/or convenience of drug administration, including controlled
5 infusion devices (e.g., for patient-controlled analgesia), metered-dose inhalers and implantable pumps.

Alternative drug delivery systems are particularly important for emerging biopharmaceuticals, which represent the most active area of therapeutic market growth and product
10 innovation. The vast majority of approved and pending biopharmaceuticals are recombinant peptides and proteins that cannot be efficiently administered orally and may be either ineffective, preclusively inconvenient or otherwise unacceptable as injectibles. The commercial potential of such
15 compounds and the rate of market development will depend in large part on improved drug delivery systems.

Drug delivery systems are defined herein as dosage forms (comprising one or more drugs) that provide increased control over drug concentration and/or duration of action either
20 systemically or at anatomically or pathophysiologically defined sites. Primary approaches being developed include controlled release formulations, local delivery of drugs in biocompatible matrices, targeted delivery using receptor- or
membrane-directed agents and prodrug compositions that remain
25 therapeutically inactive until converted to active drug *in vivo*.

Local delivery is intended to provide a therapeutically effective concentration of drug at the desired site of action for a clinically appropriate period of time without the
30 toxicity and side effects that might result from systemic administration. Representative indications include periodontal diseases, ophthalmic infections and a variety of cancers. Approaches in development include bioerodable polymers, gels, foams, microparticles, microvesicles, proteinaceous matrices
35 and implantable pumps. Most local delivery approaches include a built-in sustained release mechanism to provide prolonged action following administration. However, local delivery

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requires convenient access to the site of interest, preferably either by noninvasive techniques or an otherwise-indicated surgical procedure. Further, local delivery fails to provide diffuse or systemic protection, as may be important in
5 metastatic disease, fulminant infections or other conditions prone to migration from a primary site.

Controlled release formulations are designed to maintain drug concentrations within the therapeutic range without the dramatic peak-to-trough variability that occurs with
10 conventional administration. Elimination of peak levels improves drug safety by reducing toxicity and side effects. Avoiding troughs obviates the risk of symptoms being unmasked during periods of subtherapeutic drug levels. Most controlled release technologies incorporate a sustained release mechanism
15 that provides for prolonged action of drugs with short half-lives, thereby increasing dosage intervals, ease of use and patient compliance. Prodrugs represent a special category of controlled release formulations, wherein the drug composition is inactive as administered, but is converted to
20 active form in vivo through exposure to a particular physiologic environment or metabolic process. Controlled release has been successfully used to increase the bioavailability of orally administered drugs, to minimize fluctuations in systemic drug levels, to provide coarse control
25 over biodistribution and to increase the half-life of drugs administered both locally and systemically. A major shortcoming of controlled release formulations, however, is the limited extent to which drug disposition can be practically controlled through nonselective mechanisms.

30 Drug targeting refers to preferential delivery of therapeutic agents to clinically relevant organs, tissues, cells or receptors. Preferential delivery is achieved either through specific molecular targeting agents or through methods that alter the physicochemical properties of a drug so as to
35 alter its pharmacokinetic properties and biodistribution. Specific molecular targeting agents such as monoclonal antibodies, lectins, peptides and specific sugars selectively

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bind to pathophysiologic receptors, thereby bringing a conjugated drug into close proximity with its site of action. Altering the physicochemical properties of a drug or drug-carrier complex can nonselectively influence drug distribution through effects on binding and uptake by different cell types and transport across physiologic barriers such as the gastric mucosa, skin, capillary membrane and blood-brain barrier. Examples of targeting approaches include immunoconjugates and monoclonal antibody-modified liposomes designed to specifically bind clinically significant receptors or disease markers and drugs conjugated to carriers or delivered in vehicles that enhance membrane permeability. However, such therapeutic conjugates have yet to be widely accepted. Aside from technical challenges related to tissue penetration, stability and immunogenicity, a problem with immunoconjugates and related targeting strategies is that they do not increase the percent of administered drug that gains access to the desired site of action. Affinity-based targeting agents increase the probability that a drug near its site of action will exert an effect, but they fail to increase the percentage of administered drug that reaches the desired site. Accordingly, these agents do not provide a mechanism to sequester or concentrate drug at the desired site of action. Affinity-based delivery vehicles in development provide only for partitioning of drug conjugates between bound (e.g., to targeted receptors) and free (e.g., in extracellular fluid) phases, which partitioning is directly dependent on the bulk concentration of drug conjugate. The efficiency of delivery is therefore limited both by the affinity of the targeting agent for its receptor and by the percentage of administered drug that distributes to therapeutically relevant sites. In general, treatment of localized conditions such as cancers, infections and vascular occlusions by systemic administration of therapeutic immunoconjugates is highly inefficient. Only a small fraction (<1%) of administered conjugate interacts with targeted receptors, the remainder being metabolized and excreted.

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Accordingly, there is a growing need for drug delivery systems that provide greater efficiency, safety, duration of action and convenience than current drug targeting methods.

SUMMARY OF THE INVENTION

5 An object of the present invention is to provide a prodrug complex comprising a drug specifically bound to a synthetic receptor, wherein the specifically bound drug becomes therapeutically active only upon dissociation from the synthetic receptor.

10 Another object of the present invention is to provide a prodrug complex comprising a drug specifically bound to a synthetic receptor, wherein the *in vivo* half-life of the prodrug complex is greater than the *in vivo* half-life of the drug administered in unbound form.

15 Another object of the present invention is to provide a prodrug complex comprising a biopharmaceutical specifically bound to a synthetic receptor, wherein the *in vivo* stability of the biopharmaceutical is increased when it is specifically bound to the synthetic receptor.

20 Another object of the present invention is to provide a multi-prodrug reservoir comprising multiple drug molecules specifically bound to a heteropolymer, wherein the drug molecules are specifically bound at a repeating synthetic receptor motif comprising a monomer sequence selected by
25 combinatorial methods.

Another object of the present invention is to provide an immobilized prodrug complex comprising a drug specifically bound to a synthetic receptor which is operatively attached to a biologic or biocompatible structure, wherein the *in vivo*
30 half-life of the immobilized prodrug complex is greater than the *in vivo* half-life of either the prodrug complex or the drug administered alone.

Another object of the present invention is to provide a method for modulating the transport of a drug across a biologic
35 membrane by administering the drug in the form of a prodrug complex or immobilized prodrug complex.

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Another object of the present invention is to provide a method for increasing the duration of action of an administered dose of drug by administering the drug in the form of a prodrug complex or immobilized prodrug complex.

5 Another object of the present invention is to provide a method for increasing the percentage of an administered dose of drug that interacts with its therapeutic receptors by administering the drug in the form of a prodrug complex or immobilized prodrug complex.

10 Another object of the present invention is to provide a method for reducing the physiologic concentration of drug available for nonspecific interactions following administration of a therapeutically effective dose by administering the drug as a prodrug complex or immobilized prodrug complex.

15 Another object of the present invention is to provide a method for regulating the rate of drug delivery in proportion to the number, concentration or activity of targeted receptors by administering the drug as a prodrug complex or immobilized prodrug complex.

20 Another object of the present invention is to provide a method for reducing the frequency of administration, cumulative dose, toxicity and side effects of a drug without decreasing therapeutic efficacy by administering the drug as a prodrug complex or immobilized prodrug complex.

25 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods, compositions and applications for efficient, site-specific drug delivery using prodrug or multi-prodrug complexes comprising therapeutic agents specifically bound to synthetic receptors. Preferred
30 embodiments of these complexes enhance drug delivery by providing for increased specificity, efficiency and duration of therapeutic action over conventional pharmaceutical formulations and emerging methods for drug targeting such as immunoconjugates, fusion proteins, and liposomes, and
35 controlled drug delivery such as microparticles, bioerodable polymers, gels, and foams. In addition, binding of a selected

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drug to a synthetic receptor provides increased stability to the selected drug, thereby also enhancing drug delivery. These complexes comprise drugs or known chemical entities that remain substantially inactive or unavailable in the absence of a targeted pathophysiologic receptor to which they specifically bind with relatively high affinity. In the presence of such pathophysiologic receptors, drug dissociation and rebinding results in target-dependent delivery of drug from synthetic receptors to pathophysiologic receptors. Therapeutic benefits are achieved through administration of a prodrug complex or multi-prodrug complex of the present invention comprising at least one drug molecule specifically bound to at least one synthetic receptor.

For the purposes of the present invention, "drug" is meant to include any molecule, molecular complex or substance administered to an organism for diagnostic or therapeutic purposes, including medical imaging, monitoring, contraceptive, cosmetic, nutraceutical, pharmaceutical and prophylactic applications. The term "drug" is further meant to include any such molecule, molecular complex or substance that is chemically modified and/or operatively attached to a biologic or biocompatible structure. The term "prodrug" refers to a drug, drug precursor or modified drug that is not fully active or available until converted *in vivo* to its therapeutically active or available form. The term "prodrug complex" refers to a prodrug comprising at least two noncovalently bound molecules and includes, without limitation, a drug specifically bound to a synthetic receptor. The term "multi-prodrug complex," also described herein as a "multi-prodrug reservoir," refers to a prodrug complex comprising at least two drug molecules specifically bound to at least two synthetic receptors. The terms "specifically bind," "specifically bound" and "specific binding" refer to saturable, noncovalent interaction between a ligand and a receptor that can be competitively inhibited by structural analogs of the ligand. The terms "dissociable" and "displaceable" refer to specifically bound ligand-receptor complexes capable of undergoing net dissociation in the

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presence of a second specific binding partner for either the ligand or the receptor of said ligand-receptor complexes. The term "ligand" refers to a specific binding partner of a receptor and includes, without limitation, receptor agonists, partial agonists, mixed agonists, antagonists, drugs, hormones, transmitters, autocoids, growth factors, cytokines, prosthetic groups, coenzymes, cofactors, regulatory factors, antigens, haptens, vitamins, nucleic acids and synthetic heteropolymers comprising amino acids, nucleotides, carbohydrates or nonbiologic monomers, including analogs and derivatives thereof, and conjugates or complexes formed by attaching or binding any of these molecules to a second molecule. The term "receptor" refers to a specific binding partner of a ligand and includes, without limitation, membrane receptors, soluble receptors, cloned receptors, recombinant receptors, hormone receptors, drug receptors, transmitter receptors, autocoid receptors, cytokine receptors, antibodies, antibody fragments, engineered antibodies, antibody mimics, molecular recognition units, adhesion molecules, agglutinins, integrins, selectins, nucleic acids and synthetic heteropolymers comprising amino acids, nucleotides, carbohydrates or nonbiologic monomers, including analogs and derivatives thereof, and conjugates or complexes formed by attaching or binding any of these molecules to a second molecule. The term "specific binding pair" refers to a ligand and a corresponding receptor. The term "synthetic receptor" refers to any naturally occurring, recombinant, biologically produced or synthetic ligand or receptor which is designed, selected or engineered to specifically bind a drug. The terms "therapeutic receptor" and "pathophysiologic receptor" refer to the molecular site of drug action. The term "therapeutic target" refers to an object of therapeutic intervention, including any physiologic or pathologic entity comprising therapeutic receptors, such as a specified organ, tissue or type of cell, platelet, corpuscle, microorganism, molecular complex or molecule. The term "biocompatible" refers to an exogenous substance that is nonimmunogenic, nonallergenic and nontoxic when administered *in vivo*.

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In contrast to existing methods that rely upon either active or passive drug targeting or controlled drug delivery, including sustained release, prolonged action and repeat action formulations, the complexes of the present invention rely upon drug partitioning through differential affinity for a synthetic receptor versus the targeted pathophysiologic receptor. The present invention entails administration of drug prebound to a specific binding partner, partitioning of drug between synthetic receptors and therapeutic targets, and target-dependent availability of active drug, thereby providing for specific partitioning of a single ligand between different receptors. The invention can be further improved for certain applications by operative attachment of a synthetic receptor to a biologic or biocompatible structure to either the synthetic receptor or the drug. By operative attachment, it is meant that the synthetic receptor may be either directly attached to said structure or indirectly attached through an intermediate (e.g. a carrier, drug or spacer), and the attachment may be either covalent or noncovalent. It will be apparent to those of skill in the art that covalent attachment of a selected drug or synthetic receptor requires chemical modification, which may include introduction of new groups, modification, transformation or blocking of groups, attachment to groups, crosslinking and the like. For the purpose of this disclosure, the terms "drug" and "synthetic receptor" include drugs and synthetic receptors that have been chemically modified and/or attached to a biologic or biocompatible structure.

Synthetic receptors which are used in the prodrug and multi-prodrug complexes of the present invention can be selected and produced by a number of different methods well known to those of skill in the art including, but not limited to, monoclonal antibody technologies and combinatorial techniques for selecting heteropolymers of natural or modified amino acids, nucleotides, carbohydrates or small organic molecules from sequence and shape libraries. Screening of encoded chemical libraries, for example, has been used to identify synthetic receptors capable of binding to various

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large and small molecules. See, e.g., Kauffman, S. Ber. Bunsenges. Phys. Chem. 1994 98:1142-1147; Kenan et al. TIBS 1994 19:57-64; Ostresh et al. Proc. Nat'l. Acad. Sci USA 1994 91:11138-11142. The present invention applies such techniques to the selection of synthetic receptors useful in prodrug complexes that provide for improved drug delivery. Synthetic receptors are identified through iterative screening and selection for specific binding attributes and physicochemical properties, preferably from a diverse pool of molecular candidates and more preferably from a combinatorial shape library. Classes of molecules (and corresponding mimetics) from which synthetic receptors may be selected include, without limitation, antibodies and engineered antibodies, oligonucleotides, oligosaccharides, peptides, organic polymers such as polyhydroxyalkanoates, polyphenols, polyphosphates and polysulfates, and derivatives, analogs or combinations thereof. Optimization of the solubility and circulating half-life of the prodrug complex is achieved through multifactorial selection from panels of synthetic receptors differing in molecular size and net charge (e.g., degree of ionization under physiologic conditions). The pharmacologic half-life of dissociable drug is maximized by further selecting synthetic receptor candidates on the basis of relative affinity for the drug compared with the apparent affinity of the drug for isolated targeted pathophysiologic receptors.

In a preferred embodiment, the prodrug complex of the present invention may further be operatively attached to a carrier. This may be achieved by first attaching either the drug or the synthetic receptor to a carrier and then specifically binding the complementary specific binding partner. Alternatively, the drug and synthetic receptor may first be specifically bound to one another to form a prodrug complex which is then operatively attached to a carrier. The carrier may be any biologic or biocompatible molecule, molecular complex or microstructure which is cleared less rapidly than free drug, preferably a cell, vesicle, microparticle, polymer, gel or matrix and more preferably a

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blood forming element or reticuloendothelial cell. As will be understood by those skilled in the art, a carrier may be attached to either the drug or synthetic receptor prior to or after formation of the prodrug complex. Benefits over
5 alternative drug delivery technologies include improved safety, efficacy and patient compliance, more convenient dosing schedules and reduced treatment costs.

Formation of quasi-stable complexes of specific binding partners that are subsequently displaced in an
10 analyte-dependent manner has been demonstrated in immunodiagnostic products. See, e.g., U.S. Patent 5,028,535; Hinds et al. *Clinical Chemistry* 1984 **30**:1174-1178; Matsui et al. *Science* 1991 **254**:1788-1791. The present invention applies quasi-stable complexes of drugs and synthetic receptors to
15 therapeutic compositions and drug delivery methods.

Protection of biopharmaceuticals such as oligonucleotides against enzymatic degradation has been achieved by covalently attaching conjugate groups near the enzyme recognition site. Synthetic receptors of the present invention can be
20 noncovalently bound to biopharmaceuticals at sites that occlude enzyme access. The term "biopharmaceutical" includes drugs that are either produced biologically or synthesized from carbohydrates, amino acids, lipids, nucleotides or derivatives or analogs thereof. Prodrug complexes of the present invention
25 thereby provide a versatile method for protecting biopharmaceuticals from enzymatic degradation thus enhancing drug delivery.

Operative attachment of ligands to cells, liposomes, microparticles and other structures has been applied to both
30 immunodiagnostic tests and drug delivery. See, e.g., O'Connell et al. *Clinical Chemistry* 1985 **31**:1424-1426; Szabo, G. and Damjanovich, S. *Cytometry* 1989 **10**:801; Betageri, G.V. and Habb, M.J. *Pharmaceutical Engineering* 1994 **14**:8-16. *Ex vivo* modification of erythrocytes and lymphocytes for subsequent
35 diagnostic and therapeutic use has also been demonstrated, as has stabilization of liposomes for prolonged-action drug delivery. In the present invention similar techniques are

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applied to development of microcarrier-immobilized prodrug complexes that release active drug in proportion to the availability of therapeutic receptors, rather than passive release or delivery at a predetermined rate.

5 Biocompatible matrices and microparticles have been developed for therapeutic implants, prosthetic devices and controlled drug delivery. The present invention provides methods and compositions that use such biocompatible structures as carriers for controlling the distribution and half-life of
10 novel prodrug complexes. Preferably, compositions include biopolymers and synthetic organic equivalents comprising repeating synthetic receptor motifs within heteropolymers of different size and shape that can be synthesized with defined and reproducible molecular composition. Linear, branched and
15 cyclized biopolymers comprising nucleotides, amino acids, saccharides, fatty acids, phenols, phosphates, sulfates and/or other organic monomers arranged with repeating sequences can be preselected for specific binding to drugs of interest.

An important advantage of the present invention is the
20 versatility which permits an array of compositional permutations from which to select and optimize specific embodiments for different clinical indications, drug classes, target distribution and pharmacokinetic objectives. For example, a first embodiment involves use of drugs in
25 specifically bound form, wherein the selected synthetic receptor serves to minimize nonspecific binding of the drug to low affinity sites and protects against unwanted cellular uptake and metabolic degradation. Because the drug's active site is specifically bound to a synthetic receptor, the
30 drug-partner complex is functionally inactive until drug is released to a therapeutic receptor and therefore fits the definition of a "prodrug." In this embodiment, different synthetic receptor design and selection strategies are required depending on the drug of choice, the preferred duration of drug
35 action, and the physioanatomic distribution and microlocalization of therapeutic targets.

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Using this embodiment, the safety and duration of action of a conventional pharmaceutical can be improved. For example, use of this complex with a drug for which clinical utility is limited by toxicity, side effects, inconvenient dosing and/or associated patient noncompliance can minimize peak-to-trough fluctuations, reduce adverse effects and sustain therapeutic action of a systemically administered drug. Examples of drugs for which this complex is especially suited include, but are not limited to: anti-infectives that bind to membranes of sensitive organisms such as polyene antifungals and glycopeptide antibiotics or are internalized by receptor-mediated processes such as isoniazid, aminoglycosides, and tetracyclines; allergy, asthma and ulcer drugs that act at receptors for histamine, such as terfenadine and cimetidine and other autocooids such as bradykinins, prostacyclins, serotoninins, and leukotrienes; cardiovascular drugs and antihypertensives such as cardiac glycosides, ACE inhibitors, beta-blockers and calcium antagonists; antithrombotics such as thrombin inhibitors and platelet receptor antagonists. This type of prodrug complex is designed to release active drug to extracellular or external membrane receptors such that therapeutic action does not require cellular uptake. In addition, the selected synthetic receptor enhances cellular uptake of specifically bound drug relative to free drug, thereby favoring drug action on intracellular receptors.

A second embodiment, further involves operative attachment of specifically bound drug-partner complexes to blood forming elements, reticuloendothelial cells or long half-life, biocompatible microstructures (e.g., liposomes, microspheres) or nanostructures (e.g., biopolymers, multimolecular complexes). This embodiment provides a method to continuously perfuse therapeutic targets with high capacity microreservoirs of inactive prodrug complexes in such a manner that active drug dissociates in proportion to therapeutic receptor levels. The circulating half-life and biodistribution of carrier-bound prodrug complexes can be optimized for different applications by selecting carriers with different

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physical and chemical properties (e.g., size, shape, degree of ionization, lipid solubility).

In a preferred embodiment, preselected synthetic receptors are built into a biocompatible carrier such as a biopolymer comprising sequences of monomers (e.g., nucleotides, amino acids, saccharides, fatty acids, phenols, phosphates, sulfates) arranged as repeating synthetic receptor motifs. In this preferred embodiment, multiple drug molecules specifically bind to a biopolymer comprising multiple synthetic receptors to form a multi-prodrug complex.

Another embodiment of the present invention, involves operative localization of prodrug complexes to a given site, tissue, fluid space or cavity which is accessible either noninvasively, by injection or during endoscopy, catheterization or surgical procedures. Prodrug complexes can be attached either directly to cell membranes or to implants or biocompatible matrices deposited or injected at the site of interest. This embodiment enables sustained retention of prodrug complexes at or near a site of localized injury, infection, inflammation, disease or dysfunction with continuous dissociation of active drug in proportion to the local concentration of therapeutic targets.

The prodrug complexes of the present invention are useful in achieving therapeutically effective drug concentrations at defined targets including organs, tissues, cells, receptors or pathologic sites, safely and cost-effectively. These complexes are also useful in eliminating peak to trough fluctuations in drug levels characteristic of intermittent dosing, thereby circumventing the risk of subtherapeutic and toxic phases. In addition, by using these complexes, therapeutic levels at desired sites are sustained for clinically effective periods of time. Further, use of these complexes minimizes exposure of nonpathologic sites to therapeutic agents, thereby reducing the incidence of toxicity and side effects.

Other fields of use for the complexes of the present invention will be obvious to those of skill in the art upon this disclosure and include, but are not limited to, cosmetics,

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nutraceuticals, medical imaging, agriculture (e.g., pesticides, fertilizers, herbicides and agriceuticals) industrial processing (e.g., food and beverages, biologicals and biotechnology-derived products) and environmental remediation.

5 The following nonlimiting examples are provided to further illustrate the present invention.

EXAMPLES

Example 1: Prodrug Complex comprising Amphotericin B

10 The advantages of these complexes will vary depending on the particular indication and corresponding drug of choice. For a drug such as amphotericin B, primary advantages relate to safety, solubility and duration of therapeutic action. Amphotericin B has been in clinical use for over thirty years and, despite toxicity problems, remains the drug of choice for
15 systemic fungal infections. One of its most serious adverse effects is renal toxicity, which occurs in up to one-third of patients receiving therapeutically effective doses. Amphotericin B is insoluble in water, requiring controlled infusion of a colloidal suspension in neutral dextrose solution
20 and precautionary monitoring of intravenous lines to ensure patency. To address toxicity and infusion problems, liposomal and/or "lipid complex" formulations of amphotericin B are being developed. Amphotericin B is believed to act by mechanically disrupting cell membranes following preferential binding to
25 ergosterol-containing fungal plasma membranes as opposed to cholesterol-rich mammalian cell membranes. Accordingly, the prodrug complex of the present invention provides a means for increasing selectivity for fungi by specifically partitioning drug from synthetic receptors to ergosterol-containing
30 membranes, thereby reducing toxic effects on mammalian cells. Selection of a suitably hydrophilic (ionized) synthetic receptor also provides a stable, soluble dosage form to overcome the inconvenience, cost and risk of controlled infusion.

35 A prodrug complex comprising amphotericin B specifically bound to a synthetic receptor comprising amino acids,

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nucleotides, sugars and/or other small organic monomers is formulated.

Synthetic receptors useful in this formulation are identified through iterative screening and selection for specific binding attributes and physicochemical properties, preferably from a diverse pool of molecular candidates and more preferably from a combinatorial shape library. Classes of molecules (and corresponding mimetics) from which synthetic receptors may be selected include, without limitation, antibodies and engineered antibodies, oligonucleotides, oligosaccharides, peptides, organic polymers such as polyhydroxyalkanoates, polyphenols, polyphosphates and polysulfates, and derivatives, analogs or combinations thereof. Optimization of the solubility and circulating half-life of the prodrug complex is achieved through multifactorial selection from panels of synthetic receptors differing in molecular size and net charge (e.g., degree of ionization under physiologic conditions). The pharmacologic half-life of dissociable drug is maximized by further selecting synthetic receptor candidates on the basis of relative affinity for amphotericin B compared with the apparent affinity of the drug for isolated fungal membranes.

Example 2: Prodrug Complex for stabilizing HIV aptamer

The *in vivo* half-life and efficacy of a biopharmaceutical can be improved using prodrug complexes of the present invention. Biopharmaceutical classes amenable to this embodiment include, but are not limited to, peptides (e.g., hormones, releasing factors, molecular recognition units), proteins (e.g., monoclonal antibodies, recombinant antigens, hormones, interferons, colony stimulating factors), oligonucleotides (e.g., antisense, ribozymes, aptamers), oligosaccharides (e.g., cell adhesion molecules, immunomodulators, anti-infectives) and hybrid structures such as glycopeptides and glycolipids.

For example, an aptamer that specifically binds and inhibits HIV reverse transcriptase is protected against

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enzymatic degradation by administration in specifically bound form. The specific binding partner of the anti-HIV aptamer may be either a synthetic receptor selected from a combinatorial shape library or an oligonucleotide that hybridizes to the aptamer through Watson-Crick base pairing with a suitable degree of complementarity to yield quasi-stable hybrids that are dissociable in the presence of HIV reverse transcriptase. These oligonucleotides are generated by *in vitro* evolution from initial sequence segments complementary to different nucleotide sequences of the anti-HIV aptamer. In this embodiment, at least one HIV aptamer is selected for specific binding to a relatively conserved region of HIV reverse transcriptase from a randomized pool or combinatorial shape library comprising oligonucleotides generated by *in vitro* evolution. Potentially useful shape libraries include, without limitation, populations of polymeric conformers prepared from random combinations of amino acids, nucleotides, carbohydrates and other organic monomers. Selected synthetic receptors are first evaluated *in vitro* for effectiveness in protecting aptamers against enzymatic degradation through stability studies of corresponding prodrug complexes and control (unbound) aptamers. Synthetic receptors affording protection are then tested for their ability to efficiently deliver aptamers to therapeutic targets *in vitro*. Prodrug complexes comprising each selected aptamer specifically bound to each selected synthetic receptor are incubated alone and in combination with isolated preparations of HIV reverse transcriptase, and the rate, degree and duration of enzyme inhibition are compared with control conditions (enzyme alone, enzyme plus aptamer(s), enzyme plus synthetic receptor(s)). Selected prodrug complexes and combinations are then tested for safety and efficacy in preclinical and clinical studies.

Example 3: Prodrug Complex comprising antiplatelet formulations as antithrombotics

Vascular thrombotic events associated with myocardial infarction, percutaneous transluminal coronary angioplasty

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(PTCA), stroke, peripheral arterial occlusion and venous thromboembolism, among other conditions, cause significant morbidity and mortality. Intense antithrombin and antiplatelet drug development efforts are underway to reduce the incidence of thrombotic events. Because rethrombosis occurs in 15% to 35% of treated patients, a major drug development focus for the treatment of acute myocardial infarction is maintaining vessel patency following thrombolytic therapy. Another major focus is reducing the incidence of restenosis following PTCA procedures from the historical rate of about 30%. Other important applications for antithrombin and antiplatelet agents include chronic maintenance of vessel patency following coronary artery bypass surgery and post-thromboembolic stroke.

Pharmacologic approaches to thrombosis include prostaglandins, calcium channel blockers and antifibrinogen agents; antagonists of platelet activating factor and glycoprotein (Gp) Ib, IIb and IIIa receptors; ticlopidine, which alters GP IIb/IIIa receptor expression; and inhibitors of cyclooxygenase, thrombin, phosphodiesterase and thromboxane synthetase. Significant evidence indicates that fibrinogen binding to the platelet Gp IIb/IIIa (adhesion) receptor is the final common pathway of platelet aggregation, suggesting the utility of effective Gp IIb/IIIa receptor antagonists. CENTORX (Centocor; Malvern, PA) is a chimeric anti-7E3 Fab fragment with Gp IIb/IIIa receptor specificity. RGD and RGDS peptides bind the active site of the Gp IIb/IIIa receptor through the adhesive protein recognition sequences Arg-Gly-Asp and Arg-Gly-Asp-Ser, respectively, which are essential for fibrinogen-receptor interaction. However, the clinical and commercial potential of such antibodies and peptides as antithrombotics is limited by their unacceptably short half-lives. Platelet Gp Ib receptors interact with von Willebrand factor associated with damaged vascular endothelium to initiate platelet adhesion. Adhesion is followed by platelet aggregation which, in turn, leads to thrombus formation. Gp Ib receptor antagonists may therefore interrupt

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thrombus formation at an earlier point in the pathologic cascade than Gp IIb/IIIa receptor antagonists.

Administration of a drug specifically bound to an immobilized synthetic receptor as in the present invention can increase the circulating half-life and therapeutic efficacy of the drug, as exhibited by enhanced antithrombotic performance of a platelet receptor antagonist. For example, a therapeutic composition comprising a Gp IIb/IIIa receptor antagonist (e.g., RGDS peptide SK&F 106760 (SmithKline Beecham; Philadelphia, PA), Britistatin or Echistatin (both of Merck; Rahway, NJ)) specifically bound to selected synthetic receptors operatively attached to red blood cells obtained by autologous or heterologous donation. Synthetic receptors are selected for specific binding to platelet Gp IIb/IIIa receptor antagonists in accordance with methods described in Examples 1 and 2. Selected synthetic receptors are attached to red cell membranes either covalently (e.g., by chemical conjugation) or by noncovalent partitioning into the lipid bilayer following conjugation to a lipophilic carrier (e.g., a Zyn-Linker, glycolipid or synthetic phospholipid). Red cell-prodrug complexes are then prepared by addition of the Gp IIb/IIIa receptor antagonist to synthetic receptor-modified red cells. Prodrug-modified red cells, stored at 2-8°C until use, are administered perioperatively by intravenous infusion.

Multi-prodrug complexes such as these are designed for therapeutic applications requiring prolonged therapeutic action at extracellular or external membrane receptors. Preferred embodiments favor distribution and retention of systemically administered drugs within particular physiologic compartments, such as the circulation or lymphatic system. Representative applications include, but are not limited to, cardiovascular, respiratory, endocrine, immune, hematologic and anti-infective therapeutics.

Example 4: Topical treatment of psoriasis using soluble interleukin receptors specifically bound to immobilized synthetic receptors

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Psoriasis is generally classified as an autoimmune inflammatory disorder. Although the etiology and pathogenesis have not been fully elucidated, interactions among genetic, immunologic and environmental factors appear to be important.

5 First-line therapy consists of lubricants, keratolytics and topical corticosteroids. Topical steroids are the primary treatment for mild psoriasis, but adverse effects are caused by diffusion of drug into the circulation. Severe psoriasis is not well managed by topical steroids which may induce
10 tolerance, toxicity and side effects with chronic use.

Interleukins (IL) have been implicated in the pathogenesis of psoriasis. IL-8, released during both acute and chronic phases of inflammatory diseases, causes both accumulation and activation of neutrophils which, in turn,
15 produce cytotoxic agents. IL-1, IL-4 and IL-7 have also been implicated in immune-mediated inflammatory diseases. Several companies (e.g., Repligen (Cambridge, MA), Immunex (Seattle, WA)) are developing soluble receptors of interleukins, particularly IL-1 and IL-8, as a means of scavenging released
20 cytokines and interrupting the inflammatory cascade.

The prodrug complexes of the present invention provide a means of retaining topically administered anti-cytokine agents (e.g., soluble IL receptors or receptor antagonists) in prodrug form at sites of inflammation. Dissociation of active
25 drug in proportion to local cytokine levels provides for target-dependent drug delivery.

For example, a prodrug complex comprising a soluble interleukin receptor (e.g., IL-1 receptor, IL-8 receptor) specifically bound to a selected synthetic receptor operatively
30 attached to a liposome, lipid complex or lipophilic matrix in a topical cream, ointment or gel can be formulated. Because the synthetic receptor is selected for its ability to specifically bind a pathophysiologic receptor, it is considered a ligand or interleukin mimetic.

35 Selected synthetic receptors are attached to liposomes, lipid complexes or lipid matrices either by direct covalent attachment or by noncovalent association following conjugation

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to a lipophilic carrier. Synthetic receptor-modified liposomes, lipid complexes or lipid matrices are converted to immobilized prodrug complexes by incubation with drug (e.g., IL-1 receptor, IL-8 receptor). Immobilized prodrug complexes are then incorporated into a penetrating cream, gel or ointment which is applied topically to psoriatic lesions. Locally released interleukins (having a higher affinity than immobilized synthetic receptors for soluble IL receptors) compete with immobilized synthetic receptors (prodrug complexes) for specifically bound soluble IL receptors. Released interleukins are scavenged by soluble IL receptors which dissociate from immobilized prodrug complexes, thereby preventing cytokine-mediated recruitment and activation of neutrophils and interrupting the downstream inflammatory cascade.

While treatment of psoriasis is exemplified, as will be obvious to one of skill in the art upon this disclosure, these prodrug complexes comprising a drug which is a soluble receptor specifically bound to a synthetic receptor which is a ligand are useful in treating a number of different anatomically localized conditions. Preferably, complexes of this type are used for anatomically confined conditions involving locally proliferating, released or recruited therapeutic targets. Representative applications include localized infections, inflammatory, allergic and immune disorders.

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What is Claimed is:

1. A prodrug complex comprising:
 - (a) a selected drug; and
 - (b) a selected synthetic receptor which specifically
5 binds to the selected drug with a lower binding affinity than
the selected drug for a targeted pathophysiologic receptor.
2. The prodrug complex of claim 1 wherein a biologic
or biocompatible structure is attached to the prodrug complex.
3. A multi-prodrug complex comprising:
 - (a) at least two selected drugs; and
 - (b) at least two selected synthetic receptors which
specifically bind to the selected drugs with a lower binding
affinity than the selected drugs for targeted pathophysiologic
receptors.
4. The multi-prodrug complex of claim 3 wherein a
biologic or biocompatible structure is attached to the multi-
prodrug complex.
5. A method of enhancing delivery of a selected drug
to a targeted pathophysiologic receptor for said selected drug
20 comprising:
 - (a) selecting a synthetic receptor which specifically
binds a selected drug, said synthetic receptor having a lower
binding affinity for the selected drug than a targeted
pathophysiologic receptor for the selected drug;
 - 25 (b) specifically binding the selected synthetic receptor
to the selected drug to produce a prodrug complex; and
 - (c) delivering the prodrug complex to the targeted
pathophysiologic receptor so that the selected drug dissociates
from the selected synthetic receptor and binds to the targeted
30 pathophysiologic receptor.

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6. The method of claim 5 wherein step (b) further comprises attaching a biological or biocompatible structure to the selected drug or selected synthetic receptor.

7. A method of enhancing delivery of selected drugs to
5 targeted pathophysiologic receptors for said selected drugs comprising:

(a) selecting a synthetic receptor which specifically binds a selected drug, said synthetic receptor having a lower binding affinity for the selected drug than a targeted
10 pathophysiologic receptor for the selected drug;

(b) specifically binding at least two selected synthetic receptors to two selected drugs to produce a multi-prodrug complex; and

(c) delivering the multi-prodrug complex to the targeted
15 pathophysiologic receptor so that the selected drugs dissociate from the selected synthetic receptors and bind to targeted pathophysiologic receptors.

8. The method of claim 7 wherein step (b) further comprises attaching a biological or biocompatible structure to
20 a selected synthetic receptor or selected drug.

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **Prodrug Compositions and Drug Delivery Methods using Synthetic Receptors** the specification of which:

() is attached hereto.

(XX) was filed on 02 May 1997 as Application Serial No. PCT/US97/07491.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to the patentability of this application in accordance with 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

Country	Number	Date Filed	Priority Claimed			
			Yes		No	
			Yes		No	
			Yes		No	
			Yes		No	

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented)
60/016,566	May 3, 1996	pending

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **Jane Massey Licata and Kathleen A. Tyrrell**, Registration Nos. 32,257 and 38,350, respectively, of the firm of **Law Offices of Jane Massey Licata**, 66 E. Main Street, Marlton, New Jersey 08053, and

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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